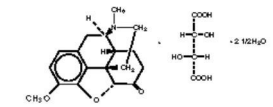
HYCOMINE - phenylpropanolamine hydrochloride and hydrocodone bitartrate syrup
Endo Pharmaceuticals Inc.

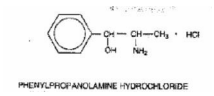
DESCRIPTION

HYCOMINE contains hydrocodone (dihydrocodeinone) bitartrate, a semisynthetic centrally-acting narcotic antitussive and phenylpropanolamine hydrochloride, a sympathomimetic amine decongestant for oral administration.

The pH of HYCOMINE and HYCOMINE Pediatric Syrup is 3.2-4.2. The hydrocodone component is (5α)-4,5-epoxy-3-methoxy-17-methylmorphinan-6-one [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) hydrate (2:5), a fine white crystal or crystalline powder, which is derived from the opium alkaloid, thebaine, and has a molecular weight of 494.50. The phenylpropanolamine component is (±)-(R*,S*)-α-(1-aminoethyl) benzenemethanol hydrochloride and has a molecular weight of 187.67. These may be represented by the following structural formulas:



HYDROCODONE BITARTRATE



PHENYLPROPANOLAMINE HYDROCHLORIDE

HYCOMINE
Pediatric Syrup
Each teaspoonful (5 mL) contains:
Hydrocodone bitartrate, USP 2.5 mg
WARNING: May be habit forming
Phenylpropanolamine hydrochloride, USP 12.5 mg
HYCOMINE Syrup
Each teaspoonful (5 mL) contains:
Hydrocodone bitartrate, USP 5 mg
WARNING: May be habit forming
Phenylpropanolamine hydrochloride, USP 25 mg

Also, HYCOMINE, both strengths, contain: artificial cherry flavor, glycerin, methylparaben, propylparaben, saccharin sodium, and sorbitol solution. HYCOMINE Pediatric Syrup contains: D&C Yellow 10 and FD&C Green 3. HYCOMINE Syrup: FD&C Red 40 and FD&C Yellow 6.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. The effects of hydrocodone in therapeutic doses on the cardiovascular system are insignificant. Hydrocodone can produce miosis, euphoria, physical and physiological dependence.

Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including 0-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites.

Phenylpropanolamine effects its vasoconstrictor activity by releasing noradrenaline from sympathetic nerve endings, and from direct stimulation of α–adrenoreceptors of blood vessels.

INDICATIONS AND USAGE

HYCOMINE (hydrocodone bitartrate and phenylpropanolamine hydrochloride) is indicated for the symptomatic relief of cough and nasal congestion.

CONTRAINDICATIONS

HYCOMINE is contraindicated in patients hypersensitive to hydrocodone or phenylpropanolamine, and in patients on concurrent MAO inhibitor therapy. Patients known to be hypersensitive to other opioids or sympathomimetic amines may exhibit cross sensitivity to HYCOMINE. Phenylpropanolamine is contraindicated in patients with heart disease, hypertension, diabetes or hyperthyroidism. Hydrocodone is contraindicated in the presence of an intracranial lesion associated with increased intracranial pressure; and whenever ventilatory function is depressed.

WARNINGS
May be habit forming. Hydrocodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of HYCOMINE and it should be prescribed and administered with the same degree of caution appropriate to the use of other narcotic drugs (See DRUG ABUSE AND DEPENDENCE).

Respiratory Depression
HYCOMINE produces dose-related respiratory depression by directly acting on brain stem respiratory centers. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated.

Head Injury and Increased Intracranial Pressure
The respiratory depression properties of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions
The administration of HYCOMINE or other narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Pediatric Use
In young children, as well as adults, the respiratory center is sensitive to the depressant action of narcotic cough suppressants in a dose-dependent manner. Benefit to risk ratio should be carefully considered especially in children with respiratory embarrassment (e.g., croup).

Phenylpropanolamine
Hypertensive crises can occur with concurrent use of phenylpropanolamine and monoamine oxidase (MAO) inhibitors, indomethacin or with beta-blockers and methyldopa.
If a hypertensive crisis occurs, these drugs should be discontinued immediately and therapy to lower blood pressure should be instituted immediately. Fever should be managed by means of external cooling.

PRECAUTIONS

General
Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of cough is identified, that modification of cough does not increase the risk of clinical or physiologic complications, and that appropriate therapy for the primary disease is provided.

Special Risk Patients
HYCOMINE should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal functions, hypothyroidism, Addison’s disease, prostatic hypertrophy or urethral stricture, asthma, narrow-angle glaucoma, and uncontrolled hypertension.

Information for Patients
Hydrocodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; phenylpropanolamine may produce a rapid pulse, dizziness or palpitations. The patient using HYCOMINE (hydrocodone bitartrate and phenylpropanolamine hydrochloride) should be cautioned accordingly.

Drug Interactions
Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with hydrocodone may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced. The use of phenylpropanolamine with other sympathomimetic amines and MAO inhibitors may produce an additive elevation of blood pressure (see WARNINGS).

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity, mutagenicity and reproduction studies have not been conducted with HYCOMINE.

Pregnancy

Teratogenic Effects: Pregnancy Category C
Animal reproduction studies have not been conducted with HYCOMINE. It is also not known whether HYCOMINE can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. HYCOMINE should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects
Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

Labor and Delivery
As with all narcotics, administration of HYCOMINE to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from HYCOMINE, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of HYCOMINE in pediatric patients under six have not been established.

ADVERSE REACTIONS

Respiratory System
Hydrocodone produces dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Cardiovascular System
Hypertension, postural hypotension, tachycardia and palpitations.

Genitourinary System
Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Central Nervous System
Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes and blurred vision.

Gastrointestinal System
Nausea and vomiting occur more frequently in ambulatory than in recumbent patients. Prolonged administration of HYCOMINE may produce constipation.

Dermatological
Skin rash, pruritus.

DRUG ABUSE AND DEPENDENCE
HYCOMINE is a Schedule III narcotic. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics; therefore, HYCOMINE should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when HYCOMINE is used for a short time for the treatment of cough. Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued oral narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy.

OVERDOSAGE

Signs and Symptoms
Serious overdosage with HYCOMINE is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest, and death may occur.
The signs and symptoms of overdosage of the individual components of HYCOMINE (hydrocodone bitartrate and phenylpropanolamine hydrochloride) may be modified in varying degrees by the presence of other active ingredients. Overdosage with phenylpropanolamine alone may result in tremor, restlessness, increased motor activity, agitation and hallucinations.

Treatment
Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdosage or unusual sensitivity to narcotics including hydrocodone. Therefore, an

appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing absorbent drug.

DOSAGE AND ADMINISTRATION

Adults: The usual dose for adults is one teaspoonful HYCOMINE Syrup (hydrocodone bitartrate 5 mg and phenylpropanolamine hydrochloride 25 mg/5 cc) every four hours as needed, not to exceed six teaspoonfuls in a 24 hour period.
Children 6 to 12 years of age: The usual dose for children 6 to 12 years of age is one teaspoonful HYCOMINE Pediatric Syrup (hydrocodone bitartrate 2.5 mg and phenylpropanolamine hydrochloride 12.5 mg/5 cc) every four hours as needed, not to exceed six teaspoonfuls in a 24 hour period.

HOW SUPPLIED

HYCOMINE Syrup (5 mg hydrocodone bitartrate, USP and 25 mg phenylpropanolamine hydrochloride, USP – per 5 mL teaspoonful) is available as an orange-colored, cherry-flavored syrup in bottles as follows:
One Pint (473.2 mL): NDC 63481-246-16
HYCOMINE Pediatric Syrup (2.5 mg hydrocodone bitartrate, USP and 12.5 mg phenylpropanolamine hydrochloride, USP – per 5 mL teaspoonful) is available as a green-colored, cherry-flavored syrup in bottles as follows:
One Pint (473.2 mL): NDC 63481-247-16
Store in controlled room temperature 15#-30#C (59#-86#F).
Oral prescription where permitted by State law.
CAUTION: Federal (USA) law prohibits dispensing without a prescription.
Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317
Manufactured by:
DuPont Pharma
Wilmington, Delaware 19880

Printed in U.S.A. 6480/August, 1997